ANTI-NMDA RECEPTOR ENCEPHALITIS: CASE SERIES AND LONG-TERM OUTCOMES

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Abstract: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a newly recognized immune-mediated encephalitis. The clinical presentations are variable, and they include behavioral change, psychosis, seizure, abnormal movement, and autonomic disturbance. Here, we report the clinical presentations and long-term outcomes of 13 Thai pediatric patients diagnosed with anti-NMDA receptor encephalitis. Three cases with unique features were identified in our series: patient 1) a young female previously diagnosed as Hashimoto encephalopathy; patient 2) a 9-year-old male presented with simple partial status epilepticus that then developed into super-refractory nonconvulsive status epilepticus; and, patient 3) a young female with delayed treatment that showed dramatic improvement. Ten patients (77%) had either complete recovery or significant clinical improvement with minimal disability after long-term follow-up. Anti-NMDAR encephalitis should be suspected in patients with clinical diagnosis of encephalitis with accompanying psychiatric symptoms, seizure, and abnormal movement. Increased awareness, early detection, and proper management portend favorable long-term outcome.

Keywords: status epilepticus, encephalitis, NMDA, Thai children

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been recognized worldwide as a new immune-mediated encephalitis since 2007 (Dalmau *et al*, 2008; Iizuka *et al*, 2008; Irani *et al*, 2010). The clinical presentations include behavioral change, psychosis, seizure, abnormal movement, and autonomic disturbance. Dalmau *et al* (2011) reported favorable outcome after appropriate treatment. Here, we describe 13 pediatric cases of anti-NMDAR encephalitis, with variability in clinical features, investigative findings, treatments, and long-term outcomes. This is the first study to investigate and report NMDA receptor encephalitis in Thai children.

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MATERIALS AND METHODS

We retrospectively reviewed all patients aged 0-15 years that were diagnosed as anti-NMDAR encephalitis at the Department of Pediatrics, Siriraj Hospital during the 1 January 2010 to 31 March 2014 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Diagnosis was based on clinical symptoms and confirmed by presence of anti-NMDAR antibody in cerebrospinal fluid (CSF) and/or serum by both immunohistochemistry assay and cell-based assay (Euroimmun AG, Luebeck, Germany) (Wandinger *et al*, 2011). For the tissue immunohistochemistry assay, mouse brain composite substrate (hippocampus, forebrain, and cerebellum) was used. Anti-NMDAR antibody was detected by fluorescence-conjugated goat antibody to human IgG. Staining patterns observed at the hippocampus and granular layer of the cerebellum were considered positive. For cell-based assay, HEK293 transfected with NR1 subunit of NMDA receptor was used as a substrate. A staining pattern on the cell surface was considered positive. Both methods were compared with a positive control. Demographic data, clinical manifestations, investigations, treatments, and outcomes were collected and analyzed.

Methylprednisolone (MP) 30 mg/kg for 3 days followed by 2 g/kg of intravenous immunoglobulin (IVIG) was given as the first-line therapy. If no clinical improvement was observed within 4 weeks, a second-line therapy consisting of either plasmapheresis or intravenous cyclophosphamide (IVCY) was given. Disease relapse was defined as recurrence of symptoms after improvement from first- or second-line therapy. All patients in this study were followed for at least 2 years to determine long-term outcome. Outcome was assessed using modified Rankin Scale (mRS) at their last visit (Table 1) (van Swieten *et al*, 1988).

RESULTS

Thirteen patients were diagnosed with NMDAR encephalitis during the study period. Median age was 12 years (range: 3-15), and 9 patients (69%) were female. Only 1 patient had underlying disease (nephrotic syndrome in patient 11). Five patients had prodromal symptoms, including headache, fever, and/or vomiting within 2 weeks before onset. The most common presenting symptoms were behavioral change (46%) and seizure (38%). Most male patients (75%) had seizure as a presenting symptom, while behavioral change and psychosis were more common in females (78%).

The clinical features of NMDAR encephalitis cases in this study are shown in Table 2.

Table 1
The modified Rankin Scale (mRS).

Score	Description
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead.

Adapted from van Swieten *et al*, 1988.

Table 2
Summarized clinical features in 13 patients with anti-NMDA receptor encephalitis.

Clinical features	No. (%)
Median age of onset (years), range	12, 3-15
Female	9 (69)
Prodromal symptom	5 (38)
Overall clinical manifestation	
Seizure	13 (100)
Behavioral change	12 (92)
Sleep disturbance	12 (92)
Abnormal movement	11 (85)
Autonomic instability	9 (69)
Hallucination	8 (62)
Median time to full symptom (days), range	20, 5-31

Seizure was found in all patients, with partial seizure reported in 8 patients and generalized seizure reported in 5. Twelve patients had behavioral symptoms, including irritability, agitation, confusion, mutism, and echolalia. Dystonia, orofacial dyskinesia, and/or chorea was found in 11 patients. Nine patients had autonomic instabilities, including hyperthermia, hypertension, bradycardia, urinary retention, and hypoventilation. Eight patients developed psychotic symptoms, such as visual, auditory, and tactile hallucination.

The following investigations were performed in all patients: cerebrospinal fluid (CSF) analysis, CSF and serum NMDA receptor antibody, electroencephalography (EEG), magnetic resonance imaging (MRI) of the brain, and tumor screening (Table 3). NMDA receptor antibodies in CSF were positive in all 13 patients, but only 7 patients (54%) had positive serum NMDA receptor antibody.

Clinical features, treatments, and outcomes in each patient are summarized in Table 4. Ten patients (77%) showed improvement after first-line therapy. Second-line therapy was given in 3 patients, with 2 patients receiving plasmapheresis and 1 patient receiving IVCY. Maintenance therapy was given in all patients. Eleven patients received azathioprine (1-3 mg/kg/day) for 5-36 months. Monthly cyclophosphamide was given in 2 patients (patient 6 had adverse effect from azathioprine, and patient 11 had nephrotic syndrome). Patients 5 and 13 developed disease relapse at 12 and 4 months, respectively; however, both patients showed improvement after reinitiation of treatment.

Three of 13 patients had unique characteristics that are described below:

Patient 1

A 14-year-old female presented with generalized tonic-clonic (GTC) seizure. She subsequently developed behavioral change, hallucination, orofacial dyskinesia, rigidity, intermittent hypertension, and tachycardia. She was previously diagnosed as Hashimoto encephalopathy after testing positive for antithyroglobulin antibody. After receiving first-line treatment, her symptoms improved and were in full remission within 5 months.

Table 3
Investigation of 13 patients with anti-NMDA receptor encephalitis.

Investigation	No. of patients (%)
CSF	
Normal finding	4 (31)
Pleocytosis	9 (69)
Median WBC (range)	13 (1-75)
Median protein (mg/dl) (range)	28 (17-58)
Negative PCR for HSV	9/9 (100)
EEG	
Generalized slow activity	8 (62)
Focal slow activity	5 (38)
Status epilepticus	2 (15)
MRI	
Abnormal (Any type)	6 (46)
Non-specific hyperintensity of white matter on T2-weighted	3 (23)
Diffuse brain atrophy	3 (23)
NMDAR antibody	
Positive serum NMDAR antibody	7 (58)
Positive CSF NMDAR antibody	13 (100)
Immune study	
Positive ANA	2/11 (18)
Positive anti-dsDNA	0/10 (0)
Positive anti-TG Ab	2/7 (29)
Positive anti-TPO Ab	1/7 (14)
Tumor screening	
Female: abnormal CT whole abdomen	0/9 (0)
Male: abnormal ultrasound testis	0/4 (0)

ANA, antinuclear antibody; anti-dsDNA, anti-double stranded DNA; anti-TG Ab, antithyroglobulin antibody; anti-TPO Ab, antithyroid peroxidase antibody; HSV, herpes simplex virus; PCR, polymerase chain reaction.

Patient 2

A 9-year-old male presented with recurrent right face and arm clonic seizures that was diagnosed as simple partial status epilepticus (SPSE). After treatment, his seizures became well-controlled and he was discharged to his home. Ten days later, he developed behavioral change, intermittent fever, GTC seizure, hypoventilation, bradycardia, blood pressure instability, and then anti-NMDAR encephalitis was diagnosed. Prolonged focal non-convulsive status epilepticus (NCSE) was developed that lasted for 5 weeks. His seizures remained refractory despite first-line treatment and several antiepileptic drugs (AEDs). Plasmapheresis, prednisolone, and azathioprine were then started. This combined therapy controlled his seizures, but he had residual right hemiparesis. At the 3-year follow-up, this patient had no neurological deficit and an intelligence quotient (IQ) of 72. He has since returned to school with some mood fluctuation.

Table 4
Clinical presentation, treatment and outcome of 13 patients with anti-NMDA receptor encephalitis.

Patient	Age (year)	Sex	First symptom	Time to treament (day)	First-line therapy	Four-week outcome	Second-line therapy	Relapse (treatment)	Maintanence therapy	Follow-up (year)	mRS score	Time to complete recovery (month)	Sequelae
1	14	F	SZ	36	MP, IVIG	Improved	-	-	AZA	5.6	0	5	-
2	9	M	SZ	35	MP, IVIG	Not improved	PP	-	AZA	4.8	1	-	Mood disorder
3	13	F	BC	570	MP, IVIG	Improved	-	-	AZA	5.3	3	-	ID, Speech problem
4	14	M	SZ	17	MP, IVIG	Improved	-	-	AZA	3.9	0	4	-
5	8	F	BC	6	MP, IVIG	Not improved	PP	+ (MP, IVIG)	AZA	4.7	3	-	ID, Mood disorder
6	10	F	PSY	33	MP, IVIG	Improved	-	-	AZA*, IVCY	4.2	0	2	-
7	14	F	PSY	45	MP, IVIG	Improved	-	-	AZA	2.2	0	3	-
8	12	M	BC	20	MP, IVIG	Improved	-	-	AZA	4.3	1	-	OCD
9	3	F	BC	47	MP, IVIG	Not improved	IVCY	-	AZA	3.9	3	-	ID
10	14	F	SZ	16	MP, IVIG	Improved	-	-	AZA	3.6	0	8	-
11	12	M	SZ	9	MP, IVIG	Improved	-	-	IVCY	3.3	0	13	-
12	12	F	BC	23	MP, IVIG	Improved	-	-	AZA	2.6	0	6	-
13	15	F	BC	24	MP, IVIG	Improved	-	+ (IVCY)	AZA	2.3	1	-	Mood disorder

AZA, azathiopine; BC, behavioral change; F, female; ID, intellectual disability; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; M, male; MP, methylprednisolone; mRS, modified Rankin Scale; OCD, obsessive-compulsive disorder; PP, plasmapheresis; PSY, psychosis; SZ, seizure.
*This patient developed pancytopenia from azathioprine.

Patient 3

A 15-year-old female presented with personality change, seizure, hallucination, dystonia, hypertension, and altered mental status. She was diagnosed as central nervous system (CNS) vasculitis. Methylprednisolone 1 g/day for 3 days was given, followed by oral prednisolone. She did not respond to treatment and she remained in an encephalopathic state. MRI of the brain that was performed 7 months after onset revealed diffuse brain atrophy. Nineteen months after onset, she developed generalized convulsive status epilepticus. She was then diagnosed as anti-NMDAR encephalitis after testing positive for anti-NMDAR antibody in both serum and CSF. First-line and maintenance treatment were given. Her symptoms gradually improved over a 4-year follow-up period. She is currently able to ambulate, follow simple commands, and perform her daily routine with minimal support.

After a long-term follow-up period that ranged from 2.3 to 5.6 years, 7 patients (54%) had complete recovery (modified Rankin Scale; mRS score = 0); 3 patients (23%) had mood/behavioral disorder or slight disability (mRS score = 1-2); and, 3 patients (23%) showed significant improvement with moderate disability (mRS score = 3). Patient 3, the patient with delayed treatment, had a long-term follow-up mRS score of 3.

DISCUSSION

The common presenting symptoms found in this study were similar to those previously reported (Titulaer *et al*, 2013). Similar to previous reports, we found that seizure more commonly presented in males and behavioral/psychotic symptoms were more commonly observed in females (Titulaer and Dalmau, 2014; Wang *et al*, 2016). In our study, some patients had only one symptom at onset. However, most (9/13) of those patients subsequently developed a variety of characteristic symptoms, including abnormal movements, behavioral changes, sleep disturbances, autonomic disturbances. Some cases in our series had unusual manifestations, and we describe those manifestations and their significance below.

Patient 1 was previously diagnosed as Hashimoto encephalopathy based on slightly high titer of antithyroglobulin, and she was treated with only corticosteroid for several weeks without clinical improvement. Xu *et al* (2011) and Guan *et al* (2015) also reported anti-NMDAR encephalitis patients with positive anti-thyroid antibody. As a result of the similarity between some immune-mediated disorders, initial symptoms and investigations may mislead us into making an incorrect diagnosis, such as a diagnosis of Hashimoto encephalopathy (Armangue *et al*, 2012). We should, therefore, carefully include and evaluate all clinical information (not only autoimmune studies) to establish an accurate diagnosis and provide appropriate treatment.

Patient 2 developed SPSE and then super-refractory focal NCSE. Status epilepticus (SE) is uncommon, but it can be found in patients with anti-NMDAR encephalitis. Dalmau *et al* (2011) reported 2 patients with refractory SE. Johnson *et al* (2010) and Kirkpatrick *et al* (2011) reported 2 young adults that presented with generalized non-convulsive status epilepticus (NCSE), and teratomas were found in both cases. Partial SE is very rare. Goldberg *et al* (2011) reported a child with focal NCSE. Kim *et al* (2015) reported a young man with unilateral NCSE. Seizures in patient 2 were finally controlled after he was treated with first- and second-line therapy, as well as multiple antiepileptic drugs. We found no tumor in this case. Significant improvement was observed after 5-year follow-up. Based on our review of the literature, this is the first report of this unique feature in children.

Patient 3 received IVIG as late as 19 months after first presentation (in early 2009), because this emerging disease was not recognized in Thailand at that time. Antibody testing for anti-NMDAR encephalitis became available in 2010.

However and in spite of the fact that her treatment was extensively delayed, she still achieved dramatic neurological improvement. A similar reversible outcome was also described in adult patients in Japan (Iizuka *et al*, 2008). Therefore, appropriate immunotherapy is essential in anti-NMDAR encephalitis, even in patients receiving delayed treatment.

From our study, CSF NMDA receptor antibodies were positive in all patients, while serum antibodies were positive in seven. This data was similar to that reported in a study by Gresa-Arribas *et al* (2014) that found 100% sensitivity for CSF antibody and 85.6% for serum. As such, CSF antibody should be investigated in all patients with suspected anti-NMDAR encephalitis. However, anti-NMDAR encephalitis should still be suspected in patients with normal CSF finding. In the present series, 4 patients (31%) had normal first CSF analysis.

Possible differential diagnoses, such as herpes simplex virus (HSV) encephalitis and other autoimmune diseases should be considered and properly evaluated. We sent CSF PCR for HSV in 9 patients and all results were negative. Autoimmune studies, such as antinuclear antibody (ANA) and antithyroglobulin, can be positive in anti-NMDAR encephalitis (Florance *et al*, 2009).

Appropriate and early immunotherapy treatment was found to be associated with lower risk of disease relapse and better outcome (Irani *et al*, 2010; Dalmau *et al*, 2011). In our case series, all patients but one (patient 3) received IVIG and pulse MP within 2 months after clinical onset. Of the 7 patients who received immunotherapy within 30 days after onset, 6 patients had improvement at 4 weeks and favorable outcome (mRS score = 0-1) at last visit. Two patients had symptom relapse despite receiving early immunotherapy, but both improved after receiving second-line immunotherapy.

Presence of tumor is associated with better outcome (Dalmau *et al*, 2011). None of our patients had ovarian or testicular tumor after 2-5 years of follow-up. A previous study reported that up to 55% of patients (mostly adults) had tumor (Dalmau *et al*, 2008). Tumor is rarely found in children, but can be found in adolescents older than 12 years and it might be detected after disease remission (Florance *et al*, 2009; Dalmau *et al*, 2011; Armangue *et al*, 2012).

In conclusion, anti-NMDAR encephalitis should be suspected in patients with clinical diagnosis of encephalitis with accompanying psychiatric symptoms, seizure, and abnormal movement. Unique features, such as SPSE, NCSE, and/or prolonged encephalopathy, may be observed. Increased awareness, early detection, and proper management portend favorable long-term outcome.

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